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New loci associated with birth weight identify genetic links between intrauterine growth and adult height and metabolism

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New loci associated with birth weight identify genetic links between intrauterine growth and adult height and metabolism

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Abstract

Birth weight within the normal range is associated with a variety of adult-onset diseases, but the mechanisms behind these associations are poorly understood¹. Previous genome-wide association studies identified a variant in the *ADCY5* gene associated both with birth weight and type 2 diabetes, and a second variant, near *CCNLI*, with no obvious link to adult traits². In an expanded genome-wide association meta-analysis and follow-up study (up to 69,308 individuals of European descent from 43 studies), we have now extended the number of genome-wide significant loci to seven, accounting for a similar proportion of variance to maternal smoking. Five of the loci are known to be associated with other phenotypes: *ADCY5* and *CDKALI* with type 2 diabetes; *ADRB1* with adult blood pressure; and *HMG2* and *LCORL* with adult height. Our findings highlight genetic links between fetal growth and postnatal growth and metabolism.

To understand further the genetic factors involved in fetal growth and its association with adult diseases, we performed an expanded genome wide association study (GWAS) of birth weight in up to 26,836 individuals of European ancestry from 18 studies (Stage 1; Supplementary Table 1; Supplementary Figures 1 to 3; see Online Methods). After follow-up analyses of 21 of the most strongly associated independent single nucleotide polymorphisms (SNPs; $P < 1 \times 10^{-5}$) in additional European samples (Supplementary Tables 2 and 3), we identified novel associations with birth weight at four loci ($P < 5 \times 10^{-8}$), and confirmed three previously reported associations²⁻⁴ (rs900400 near *CCNLI*, $P = 3.6 \times 10^{-38}$; rs9883204 in *ADCY5*, $P = 5.5 \times 10^{-20}$; rs6931514 in *CDKALI*; $P = 1.5 \times 10^{-18}$), in a joint meta-analysis of up to 69,308 individuals (Table 1; Figure 1 and Supplementary Figure 4). The index SNPs at the four newly-associated loci were rs1042725 in *HMG2* ($P = 1.4 \times 10^{-19}$), rs724577 in *LCORL* ($P = 4.6 \times 10^{-11}$), rs1801253 in *ADRB1* ($P = 3.6 \times 10^{-9}$) and rs4432842 at chromosome 5q11.2 ($P = 4.6 \times 10^{-8}$). The effect size estimates range from 0.034 SD to 0.072 SD per allele and equate approximately to changes in birth weight of 16 to 35g (Table 1). These estimates did not change materially in sensitivity analyses excluding studies with self- or parentally-reported birth weight data and those without a measure of gestational age (Supplementary Table 4).

Through the cellular mechanisms of gametogenesis and fertilization, fetal genotype is correlated with maternal genotype ($r \approx 0.5$). Using up to 11,307 mother-child pairs from a subset of studies, we found no evidence that the seven associations we observed at $P < 5 \times 10^{-8}$ are driven by the maternal, rather than the fetal, genotype (likelihood-ratio test $P > 0.05$; Table 1).

For five of the seven confirmed associations with birth weight, correspondence with GWAS findings for adult traits (type 2 diabetes, blood pressure or height) provide clues to the biological pathways involved. Two SNPs represent the same signals as known type 2 diabetes loci: *ADCY5* (previously reported²) and *CDKAL1* (previously examined in smaller candidate gene studies of birth weight³⁻⁵). We observed similar z score effect size estimates of the associations between each of these loci and ponderal index (calculated as weight/length³ to indicate neonatal leanness), birth length and head circumference (Table 1), suggesting a general effect on fetal growth. At both loci, the birth weight-lowering allele is associated with greater type 2 diabetes risk²⁻⁴. This observation is consistent with the fetal insulin hypothesis⁶, which proposes that common genetic variation influencing insulin secretion or action, both in prenatal development and adult life, could partly explain epidemiological correlations between lower birth weight and type 2 diabetes. The type 2 diabetes risk allele at *ADCY5* is associated with a number of features suggesting impaired insulin secretion: higher glucose levels after fasting and 2 hours after an oral glucose challenge^{7,8}; lower 2-hour insulin levels, adjusted for 2-hour glucose levels⁸; higher fasting proinsulin (relative to mature insulin) levels⁹; and lower Homeostatic Model Assessment (HOMA)-derived index of beta-cell function HOMA-B⁷ (Supplementary Table 5). The risk allele at *CDKAL1* is strongly associated with reduced insulin secretion in studies of adults¹⁰. Given the key role of fetal insulin in prenatal growth, we hypothesize that the *ADCY5* and *CDKAL1* risk alleles reduce fetal insulin levels, which mediate the associations with birth weight.

To investigate whether type 2 diabetes susceptibility loci other than *ADCY5* and *CDKAL1* influence fetal growth, we tested the associations between 47 additional, published type 2 diabetes loci and birth weight in our Stage 1 meta-analysis. We observed more associations with birth weight than expected by chance (Figure 2a), with 7 associations at $P < 0.05$, of which 4 achieved $P < 0.01$ (*MTNR1B*-rs1387153, *KCNQ1*-rs231362, *HHEX-IDE*-rs5015480 and *GCK*-rs4607517), including *GCK* at $P = 1 \times 10^{-4}$. Meta-analysis of the *HHEX-IDE* result with previously published data (total $n = 51,583$) strengthened the evidence of association ($P = 6.9 \times 10^{-7}$; Supplementary Table 6). The type 2 diabetes risk alleles at *HHEX-IDE* and *KCNQ1* follow *ADCY5* and *CDKAL1* in being associated with lower birth weight, providing additional support for the fetal insulin hypothesis, although the associations can only explain a small fraction of the epidemiological association.

In contrast, the type 2 diabetes risk alleles at *GCK* and *MTNR1B* were associated with higher birth weight (Figure 2b). Higher maternal glucose levels are associated with higher offspring birth weight¹¹, and both the *GCK* and *MTNR1B* loci influence fasting glucose levels throughout the normal physiological range⁷. Consistent with this, and with previous studies of the *GCK* variant¹², the effect size estimates we observed for *GCK* and *MTNR1B* were lower after adjustment for maternal genotype (Supplementary Figure 5). Well-powered studies of mothers and offspring will be required to test formally the association between maternal genotype and birth weight at these loci. The lack of a fetal association at *GCK*-rs4607517 contrasts with the strong birth weight-lowering effects of rare, heterozygous fetal *GCK* mutations¹³, and suggests that the common *GCK* variant does not influence insulin secretion until postnatal life.

The association with birth weight at *ADRB1* rs1801253 (Arg389Gly) links prenatal growth with blood pressure in adulthood since the same SNP is strongly associated with both systolic and diastolic blood pressure ($P < 5 \times 10^{-8}$)¹⁴. Epidemiological associations between birth weight and systolic blood pressure (SBP) constitute some of the strongest evidence supporting the fetal origins of adult disease¹⁵. Most studies report a linear inverse association throughout the birth weight distribution, whereby lower birth weight is associated with higher adult SBP. There is also evidence that birth weights at the high end of the distribution are associated with higher SBP¹⁶. Based on the majority of studies, we might therefore expect a fetal SBP-raising allele to be associated with lower birth weight. However, the birth weight-lowering allele at rs1801253 (Gly389) is associated with lower blood pressure in later life. We observed similar effect size estimates for associations between *ADRB1* and various birth measures (Table 1), suggesting a general effect on fetal growth. We tested for associations between birth weight and 29 additional blood pressure loci¹⁷ in our Stage 1 meta-analysis. While we did not observe strong evidence of deviation from the null (Figure 2c), associations between the SBP-raising allele and lower birth weight achieved $P < 0.01$ at *GUCY1A3/GUCY1B3*-rs13139571 ($P = 0.0008$) and *CYP17A1/NT5C2*-rs11191548 ($P = 0.009$). These were little altered on adjustment for maternal genotype (Figure 2d; Supplementary Table 7).

The associations with birth weight at the *HMGA2* and *LCORL* loci link prenatal growth with postnatal stature. At both loci, the birth weight-lowering allele is also associated with lower adult height and associations are consistent with a primary effect on birth length (Table 1). The *HMGA2* SNP is also strongly associated with birth head circumference and is known to associate with head circumference in infancy and intracranial volume in adulthood^{18,19} suggesting a general effect on growth. Variation at *LCORL* has also been associated with peak height velocity in infancy²⁰, indicating an effect on growth in childhood. When testing 178 additional published height loci²¹, we observed more associations with birth weight than expected by chance (Figure 2e), indicating that many adult height loci influence prenatal growth. Of all 180 loci, 132 show the same direction of effect size estimate with birth weight as with height (binomial sign test $P = 3 \times 10^{-10}$), although there is no strong correlation between adult height and birth weight effect sizes (Figure 2f). We did not observe any evidence that these associations were driven by maternal genotypes (Supplementary Table 8).

The remaining two loci (near *CCNLI* and on chromosome 5q11.2) are not known to be associated with any other traits. The previously reported association near *CCNLI* represents the strongest association with birth weight, and shows a strong association with ponderal index, but relatively weak associations with birth length and head circumference (Table 1), strengthening the evidence that this locus primarily acts through non-skeletal growth. In a subset of 7 studies with available postnatal data, the association had disappeared by 3 months of age (0.001 SD [95% CI: -0.030, 0.032] per rs900400 C-allele, relative to birth weight: -0.084 SD [95% CI: -0.106, -0.062]; Supplementary Table 9; Supplementary Figure 6), suggesting that the growth effects of the *CCNLI* locus are specifically intrauterine. Little is known about the birth weight locus at chromosome 5q11.2: the nearest gene, *ACTBL2*, is approximately 400kb away and has no obvious link with fetal growth. Associations at this locus are similar across the different anthropometric birth measures (Table 1) and there are no associations with adult metabolic or anthropometric traits in published studies (Supplementary Table 5).

We were interested to explore whether the same variants have any impact on birth weight in other ethnic groups. Using data from a range of non-European studies, including those of Middle Eastern, East and Southeast Asian and African origin (total $n = 11,848$; Supplementary Table 10), we showed that the 7 SNPs together explained between 0.32%

and 1.52% of the variance in birth weight, which was similar to that in Europeans (0.76%; Supplementary Table 11; Supplementary Figures 7 and 8).

To conclude, we have identified four, and confirmed three loci associated with birth weight, which explain a similar proportion of variance to maternal smoking exposure in pregnancy (Supplementary Figure 9). The associations between five of the loci and adult traits (i) highlight biological pathways of relevance to the fetal origins of type 2 diabetes, (ii) reveal complexity in that type 2 diabetes risk alleles can be associated with either higher or lower birth weight, (iii) illuminate a novel genetic link between fetal growth and adult blood pressure and (iv) demonstrate substantial overlap between the genetics of prenatal growth and adult height.

ONLINE METHODS

Stage 1: Genome-wide association (GWA) meta-analysis of birth weight: discovery studies, genotyping and imputation

We combined 18 population-based European studies with birth weight and GWA data available (total $n = 26,836$ individuals): two sub-samples from the 1958 British Birth Cohort (B58C-WTCCC, $n = 2,195$; B58C-T1DGC, $n = 2,037$); the Avon Longitudinal Study of Parents And Children (ALSPAC (Discovery); $n = 1,418$); the Children's Hospital of Philadelphia (CHOP, $n = 7,380$); the COpenhagen Prospective Study on Asthma in Childhood (COPSAC-2000, $n = 353$); the European Prospective Investigation of Cancer (EPIC, $n = 1,478$); the Erasmus Rucphen Family (ERF) study ($n = 325$); two sub-samples from the Generation R study (Generation R (Discovery 1), $n = 1,194$; Generation R (Discovery 2), $n = 1,410$); the Helsinki Birth Cohort Study (HBCS, $n = 1,566$); the Lifestyle – Immune System – Allergy (LISA) study ($n = 387$); the Northern Finland 1966 Birth Cohort (NFBC1966; $n = 4,333$); two sub-samples of singleton births from the Netherlands Twin Register (NTR1, $n = 414$; NTR2, $n = 247$); the Orkney Complex Disease Study (ORCADES, $n = 328$); the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study ($n = 368$); the Raine study (RAINE, $n = 1,105$); and the Sorbs study (SORBS, $n = 298$).

While no systematic phenotypic difference is seen between the sub-samples of the 1958 British Birth Cohort, Generation R and Netherlands Twin Register, they were analyzed separately because they were genotyped on different platforms and/or at different times.

Genotypes within each study were obtained using high-density SNP arrays and then imputed for up to ~2.7 million HapMap SNPs (Phase II, release 21/22; <http://hapmap.ncbi.nlm.nih.gov/>). The basic characteristics, exclusions applied (for example, individuals of non-European ancestry, related individuals), genotyping, quality control and imputation methods for each discovery sample are presented in Supplementary Table 1.

Statistical analysis within discovery studies

Birth weight (BW) was transformed to a z score ($[\text{BW value} - \text{mean BW}] / \text{s.d. BW}$) to facilitate comparison of the data across studies. Multiple births and, where information was available (see Supplementary Table 1), preterm births (gestational age <37 weeks) were excluded from all analyses. The association between each SNP and birth weight was assessed in each study sample using linear regression of birth weight z score against genotype using an additive genetic model, with sex and, where available, gestational age as covariables. Since gestational age was not available in all studies, we later performed a sensitivity analysis, excluding the studies that did not have this covariable (see below). The GWA analysis was performed using SNPTEST²³, mach2qt²⁴, PLINK²⁵ (<http://pengu.mgh.harvard.edu/purcell/plink/>), GenABEL²⁶ or ProbABEL²⁷. Details of any

additional corrections for study-specific population structure are given in Supplementary Table 1. The data annotation, exchange and storage were facilitated by the SIMBioMS platform (<http://www.simbioms.org>)²⁸.

Meta-analysis of discovery studies

Prior to meta-analysis, SNPs with a minor allele frequency (MAF) < 0.01 and poorly imputed SNPs (proper_info < 0.4 (SNPTEST); r2hat < 0.3 (mach2qtl)) were filtered. Genomic control (GC)²⁹ was applied to adjust the statistics generated within each cohort (see Supplementary Table 1 for individual study λ values). Inverse variance fixed-effects meta-analyses were undertaken using different software packages METAL (2009-10-10 release)³⁰ and GWAMA (version 2.0.6)³¹ by two meta-analysts in parallel and compared to obtain identical results. The meta-analysis results were obtained for a total of 2,684,393 SNPs. We applied a second GC correction to adjust the overall meta-analysis statistics ($\lambda = 1.051$) before selecting 21 SNPs for follow-up, which surpassed a P -value threshold of $P < 1 \times 10^{-5}$. This additional GC correction was, however, only applied for the purpose of choosing the arbitrary significance threshold; we report here Stage 1 P -values after only the first GC correction (see Supplementary Table 2) because a second GC correction is generally considered to be over-conservative³². We additionally selected SNP rs6537307 ($P = 4.3 \times 10^{-5}$), which is in linkage disequilibrium with a known *HHIP* height-associated variant (HapMap $r^2 = 0.58$ with rs6854783³³). Of the 22 selected SNPs, rs1004059 at *SYNP02L* ($P = 2.3 \times 10^{-6}$) was available in only 8 studies since its MAF was close to 0.01. After obtaining data from this SNP from all available Stage 1 studies, we observed a meta-analysis P -value of $P = 6 \times 10^{-5}$, and so did not consider it further.

Stage 2: Follow-up of lead signals in European studies

Twenty-one SNPs selected from the discovery meta-analysis were taken forward for either custom genotyping or analysis in studies with newly available genome-wide or CardioMetaboChip array genotyping (the latter included 6 of the 21 SNPs). If the index SNP was unavailable, this was substituted with a closely correlated proxy from the HapMap (see Supplementary Table 12). Of a total of 25 available studies (maximum combined $n = 42,519$), there were 14 studies with custom genotyping ($n = 22,569$ individuals), of which 2 studies later acquired additional *in silico* data (ALSPAC (Replication), $n = 6,315$ with GWA; NFBC1986, $n = 4,897$ with CardioMetaboChip). Eight further studies had *in silico* GWA data ($n = 13,992$ individuals) and 3 further studies had *in silico* CardioMetaboChip array data ($n = 5,958$ individuals). Details of these studies are presented in Supplementary Table 3. Since resources for custom genotyping were limited, the total number of analyzed individuals varied by SNP, with 3 SNPs analysed in available *in silico* studies only (see Supplementary Table 2). Within each study, we analysed the association between each available SNP and birth weight z score in the same way as described above for Stage 1 studies.

Combined discovery and follow-up meta-analyses

We performed fixed effects inverse variance meta-analyses of the association between each SNP and birth weight, including up to 43 discovery and follow-up samples of European descent (maximum total $n = 69,308$). Individual study results for any SNP showing strong evidence of deviation from Hardy-Weinberg Equilibrium ($P < 1 \times 10^{-4}$) were excluded. Meta-analyses were performed in parallel at two different study centres, using two software packages in parallel (METAL 2009-10-10 release³⁰ and GWAMA ver.2.0.6³¹). We used Cochran's Q test and the derived inconsistency statistic, I^2 ³⁴ to assess evidence of between-study heterogeneity of effect size. Results that crossed the widely accepted genome-wide significance threshold of $P < 5 \times 10^{-8}$ were considered to represent robust evidence of association.

Sensitivity analyses and phenotypic data quality checks

The ascertainment and availability of phenotype data varied widely among the 43 studies (see Supplementary Tables 1 and 3). For example, birth weight was measured by trained personnel in some studies, but in others was self-reported in adulthood. Gestational age was not available as a covariable in all studies. We therefore performed further analyses to verify data quality and check that the effect size estimates in our meta-analyses were not greatly influenced by poor quality data or lack of adjustment for gestational age.

To identify any studies that showed unusual relationships between birth weight and other phenotypes, we obtained from each study the percentage of variance in birth weight explained by each of sex, parity, maternal smoking, gestational age and maternal pre-pregnancy BMI as $100 \times \text{adjusted-}R^2$ value from linear regression of birth weight against each individual trait. The observed relationships between birth weight and each related trait were reasonably consistent across all of the 43 studies (see Supplementary Table 13 and Supplementary Figure 9).

To assess whether adjustment for gestational age or measurement/recall bias of birth weight influenced the associations between each of the 21 SNPs and birth weight, we repeated the fixed-effects inverse-variance meta-analyses of the European results in three different subsets of studies: (i) studies with birth weight collected by any method that adjusted for gestational age ($n = 35$); (ii) studies with measured or medical record of birth weight that adjusted for gestational age only where available ($n = 26$); (iii) studies with measured or medical record of birth weight which also adjusted for gestational age ($n = 24$). We compared the effect size estimates between each of these three meta-analyses and the overall meta-analysis result (Supplementary Table 4).

Associations between birth weight and seven confirmed loci in non-European samples of varying ancestry

Using 8 study samples of varying ancestry, we investigated the 7 loci, which showed genome-wide significant associations with birth weight in the combined meta-analysis of European discovery and follow-up studies. The 8 non-European studies were from East/Southeast Asia (Chinese and Filipino), Africa (African-American, Mandinka and Moroccan), Middle East (Arab, Turkish), and South America (Surinamese) (total $n = 11,848$; Supplementary Table 10). Samples were genotyped either by custom SNP assay (2 studies), CardioMetaboChip (1 study) or genome-wide chip (5 studies). The index SNP from the European meta-analysis was taken forward as the index SNP for the non-European analyses, and associations with birth weight were analysed as described above. If the index SNP was unavailable, it was substituted with a closely correlated ancestry-specific proxy from the 1000 Genomes Pilot 1 YRI and JPT+CHB samples (released June 2010), which was found using SNAP (<http://www.broadinstitute.org/mpg/snap/>; see Supplementary Table 12). In the 5 studies with GWA data, we considered all SNPs within 250-kb either side of the European index SNP.

We performed three analyses:

- i. **Meta-analysis of single SNP associations with birth weight:** we performed fixed-effects inverse variance meta-analyses of available studies, as described above, for each of the 7 loci.
- ii. **Ethnicity-specific regional analysis:** we performed fixed effects inverse variance meta-analyses for SNPs within the 500 kb surrounding the 7 index SNPs in an ethnicity-specific manner for $n = 2,135$ East/Southeast Asian and $n = 6,315$

African-American samples. We plotted the association results against chromosomal position using LocusZoom (<http://csg.sph.umich.edu/locuszoom/>).

- iii. **Combined genotype risk score analysis:** to assess the associations between birth weight and the 7 confirmed loci in combination, we created a risk allele count (RAC) by summing the birth-weight lowering alleles at each SNP. We performed this analysis in 7 non-European studies in which 6 to 7 SNPs were available (combined $n = 11,014$) and one representative European Stage 2 study (NFBC1986, $n = 4647$). If a SNP was missing, all individuals were assigned a value of 2*frequency (HapMap, ethnicity-specific) of the birth weight-lowering allele. We performed linear regression of birth weight z score against RAC (additive model), with sex and gestational age (where available) as covariables. A genetic risk score, weighted by effect size in Europeans, gave similar results in all non-European studies (data not shown).

Variance explained

To estimate the percentage of variation in birth weight explained jointly by the 7 confirmed birth weight loci, we obtained the adjusted- R^2 from univariate linear regression of birth weight against risk allele count in 6 non-European studies and one European study (NFBC1986).

Analysis of additional anthropometric phenotypes measured at birth: birth length, birth head circumference, ponderal index

Where available, in both Stage 1 and 2 European studies, we created within-study z scores for birth length (available from 27 studies, $n = 36,084$), birth head circumference (20 studies, $n = 23,277$), and ponderal index (calculated as birth weight/length³, 27 studies, $n = 35,836$). The z scores were calculated by the same method as was used for birth weight. We used linear regression to assess the association between each outcome and each of the 7 confirmed birth weight SNPs, with sex and gestational age (where available) as covariables. We combined the results across studies using fixed-effects inverse variance meta-analysis.

Analysis of birth weight adjusted for birth length

Where both birth weight and birth length were available, we used linear regression to assess the association between birth weight z score and the 7 confirmed birth weight SNPs, with sex, gestational age (where available) and birth length as covariables. In the same set of samples, we again performed linear regression to assess the association between birth weight z score and SNP, with only sex and gestational age (where available) as covariables to allow direct comparison of analyses with and without adjustment for birth length. Meta-analysis was performed as above.

Analysis of birth weight adjusted for maternal genotype

To assess whether the birth weight associations at the seven confirmed birth weight loci were independent of maternal genotype, we used mother-offspring pairs from up to 10 European studies with both maternal and fetal genotype available (Discovery $n = 7,879$, Follow-up $n = 3,428$, total $n = 11,307$). Within each study, we performed linear regression of birth weight z score against each of the SNPs, with sex, gestational age (where available) and maternal genotype as covariables. For direct comparison, we repeated this without maternal genotype, using only subjects for whom maternal genotype was available. Fixed effects inverse variance meta-analysis was performed to combine results across studies for (i) fetal genotype, and (ii) fetal genotype adjusted for maternal genotype. We performed a likelihood ratio test to compare the model fit before and after adjustment for maternal genotype.

Analysis of associations between known type 2 diabetes, blood pressure, height and BMI loci and birth weight

Of the seven confirmed birth weight loci, five had previously been associated with either type 2 diabetes (*CDKAL1* and *ADCY5*), blood pressure (*ADRB1*) or adult height (*LCORL* and *HMGA2*). To assess whether association with birth weight is a common feature of loci associated with these adult traits, we extracted results from our Stage 1 discovery meta-analysis for 49 published type 2 diabetes SNPs^{7,22,35-48}, 180 height SNPs²¹ and 30 blood pressure SNPs^{14,17}. To complement these analyses, we analyzed the associations between the same sets of SNPs and birth weight *z* score in $n = 5,327$ mother-child pairs from the ALSPAC study. We adjusted for sex and gestational age, recorded the results before and after adjustment for maternal genotype and compared the fit of the two models using a likelihood ratio test to assess evidence of confounding by maternal genotype. This was particularly important for the analyses of type 2 diabetes SNPs since there is evidence that at least two of the known loci influence birth weight via the maternal genotype^{49,50}. For each set of loci, we used the binomial probability (sign) test, available at <http://faculty.vassar.edu/lowry/binomialX.html>, to assess whether there was more evidence of negative or positive associations with birth weight than the 50% expected under the null.

For the *HHEX-IDE* (type 2 diabetes) locus, there are previously-published studies reporting associations with birth weight, not all of which overlap with our Stage 1 Discovery samples^{4,5}. To obtain an approximate overall result for this locus, we therefore meta-analyzed (inverse variance, fixed effects) our Stage 1 result with additional published data from the ALSPAC, Inter99 and EFSOCH studies and *in silico* data available from Stage 2 (total $n = 51,583$). Two SNPs at the locus were represented in the meta-analysis: rs111875 and rs5015480 ($r^2 = 0.97$). Since the effect sizes for the published studies were in grams, we first converted them to equivalent *z*-score values by dividing effect size estimates and 95% confidence limits by 484 (the median standard deviation of birth weight in grams, from our previous GWA study of birth weight)².

Analysis of the associations between seven confirmed birth weight loci and adult metabolic and anthropometric traits in publicly available results of GWA meta-analyses

We looked up the 7 confirmed birth weight index SNPs in publicly available published meta-analysis datasets to assess their associations with adult metabolic and anthropometric traits: (i) fasting glucose and fasting insulin⁷, (ii) fasting proinsulin⁹, (iii) triglycerides, total cholesterol, low density lipoprotein (LDL) cholesterol and high density lipoprotein (HDL) cholesterol⁵¹, (iv) height²¹ and (v) BMI⁵².

Analysis of the association between *CCNL1* and weight up to 6 months in seven studies

We used available postnatal weight data from the EFSOCH, Generation R (Discovery 1), Generation R (Discovery 2), LISA, HBCS, NFBC1966 and NFBC1986 (maximum total $n = 15,090$). Each study analysed weight data at the following time points, where available: birth; 1 (+/- 0.2) month; 2 (+/- 0.2) months; 3 (+/- 0.3) months; 6 (+/- 0.4) months. Within each study, we created weight-for-age *z* scores for each of the postnatal time points using Growth Analyser 3.0 (<http://www.growthanalyser.org>; Dutch Growth Research Foundation, Rotterdam, the Netherlands). The reference was a cohort of 475,588 children born between 1977 and 1981 in Sweden⁵³. Birth weight was analysed as described above. At each subsequent time point, we performed linear regression of weight-for-age *z* score against rs900400 genotype (or designated proxy SNP, see Supplementary Table 12), with gestational age at birth as a covariable. We combined the results across studies using fixed effects inverse variance meta-analysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Footnotes

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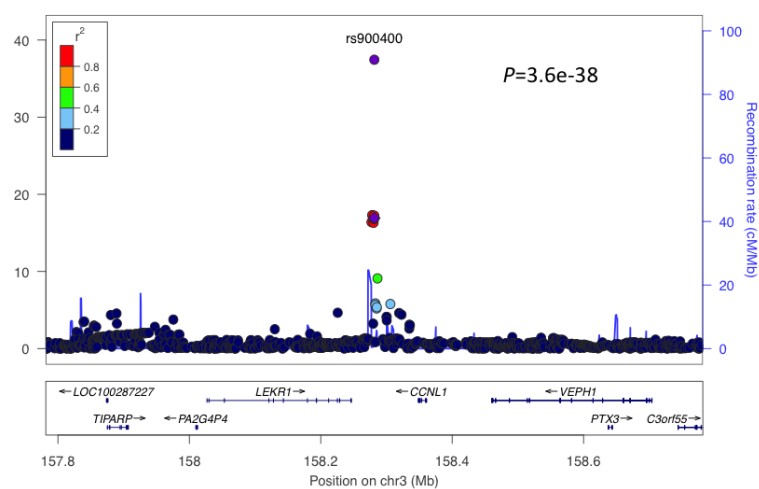
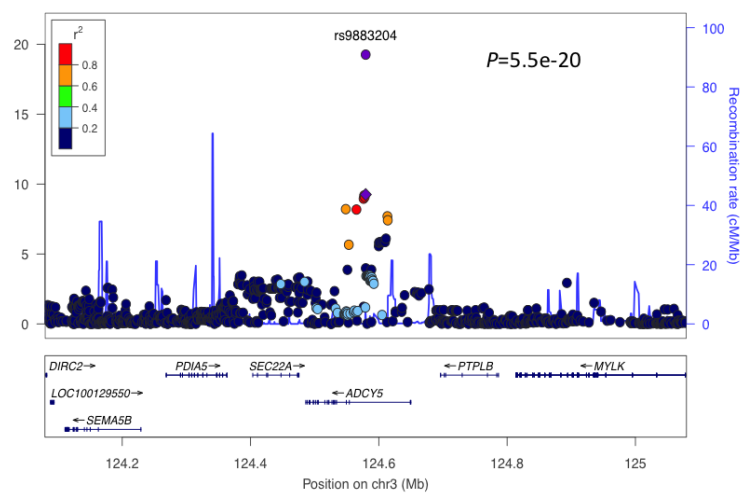
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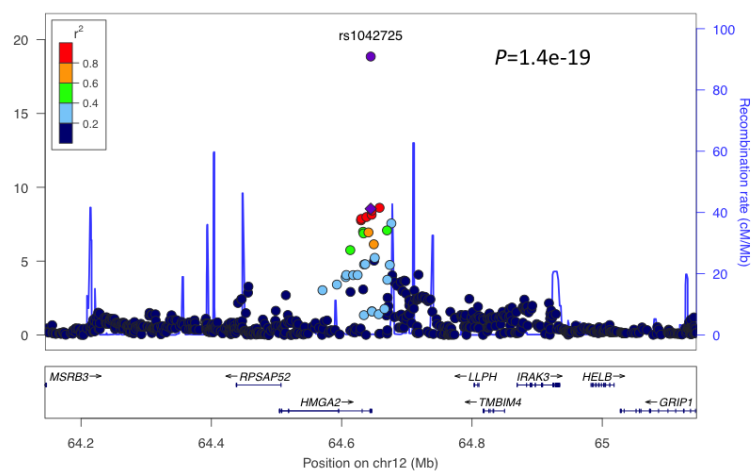
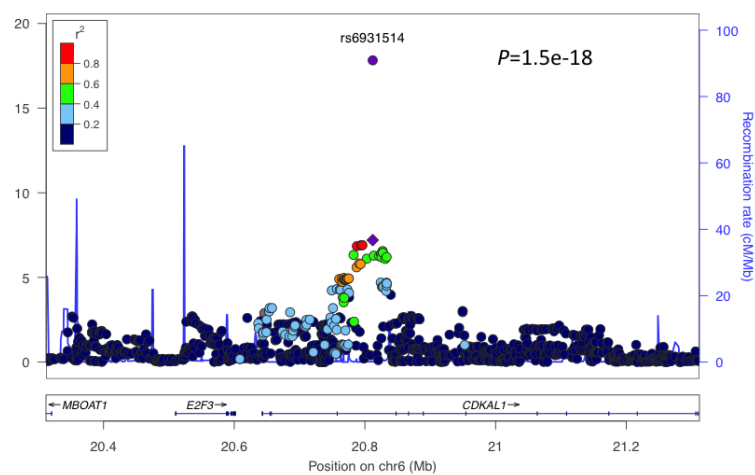
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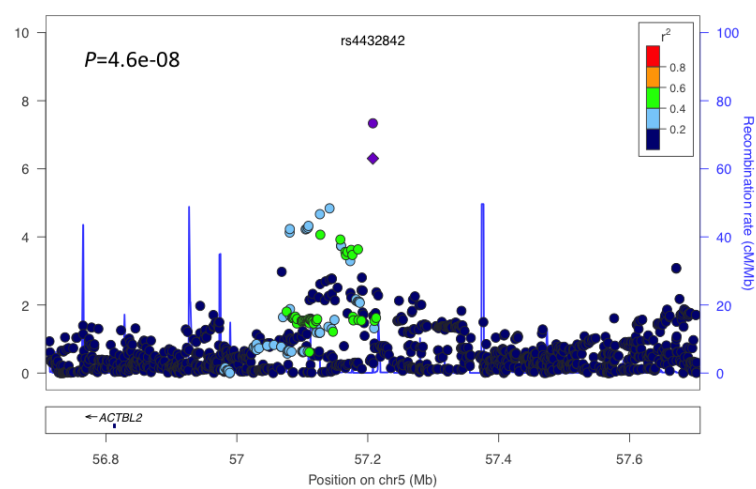
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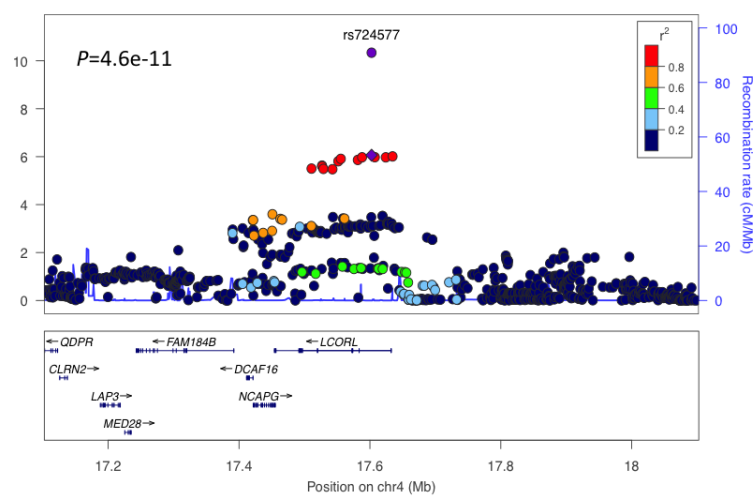
(a) *CCNL1* region(b) *ADCY5* region

(c) *HMG2* region(d) *CDKAL1* region

(e) 5q11.2 region



(f) LCORL region



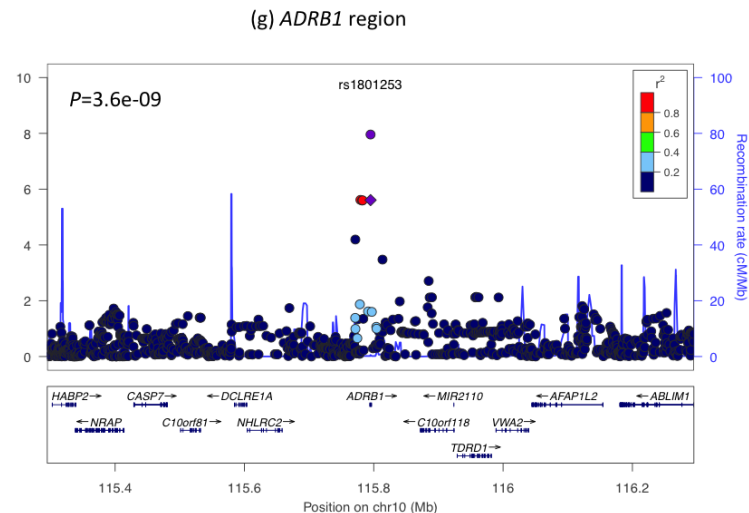
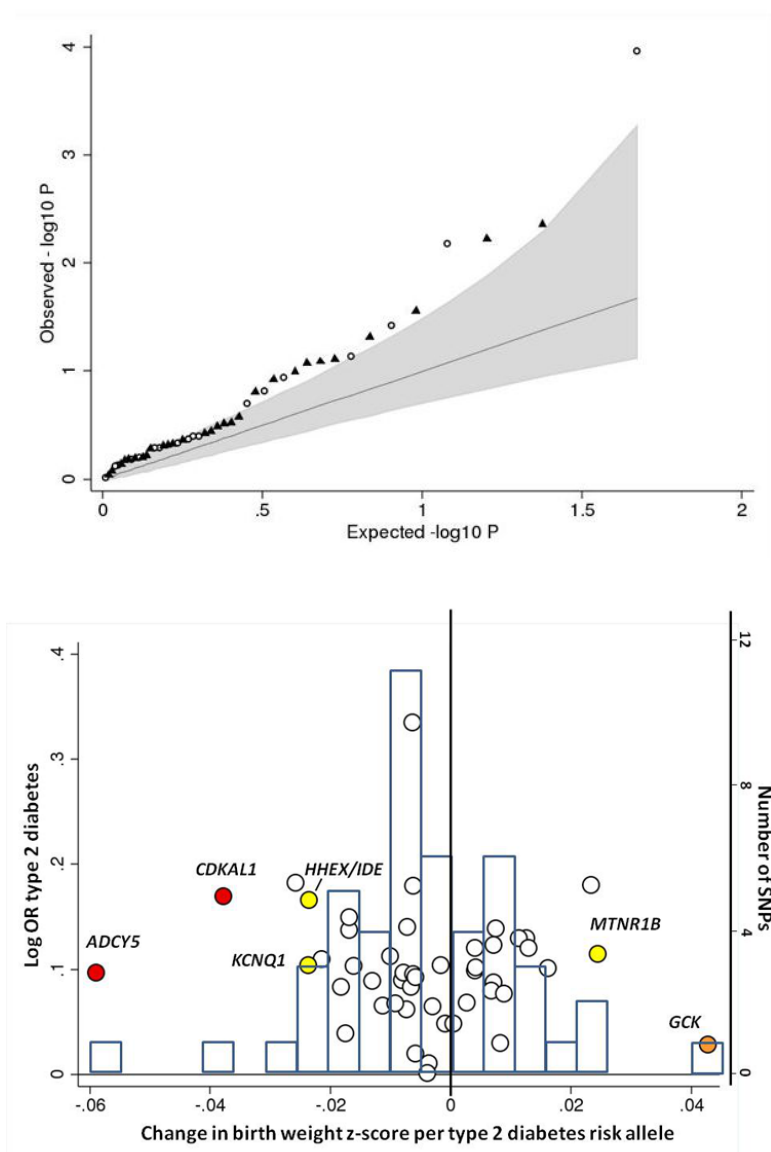


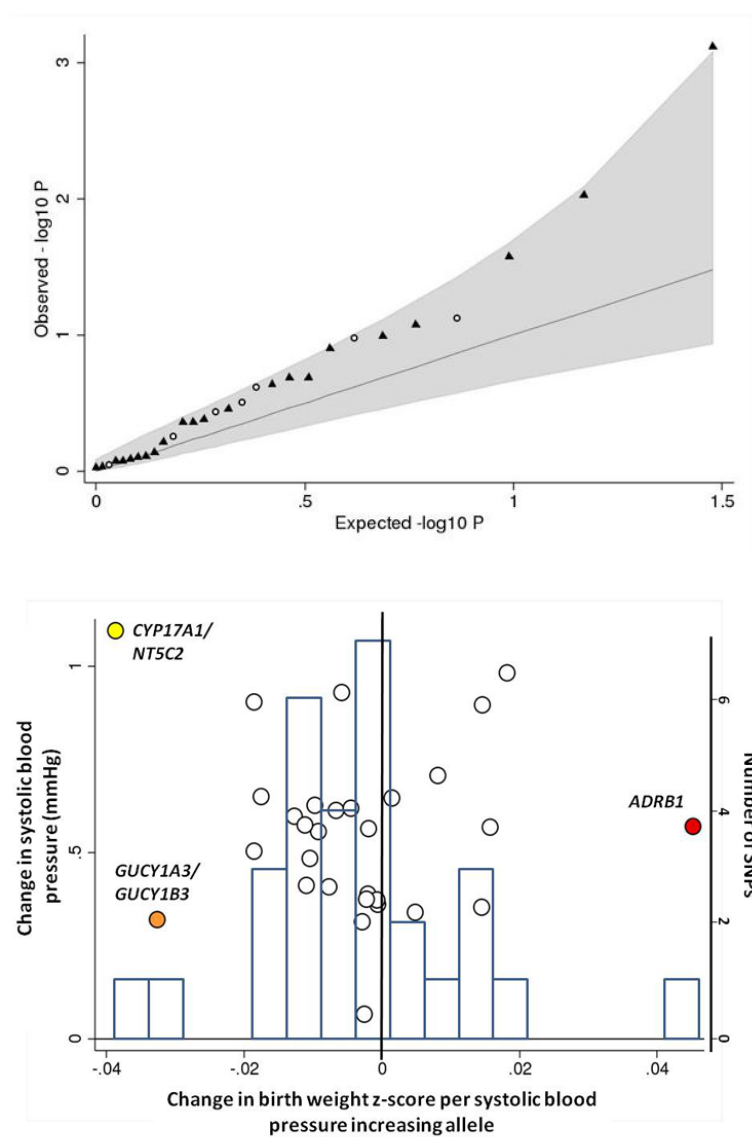
Figure 1.

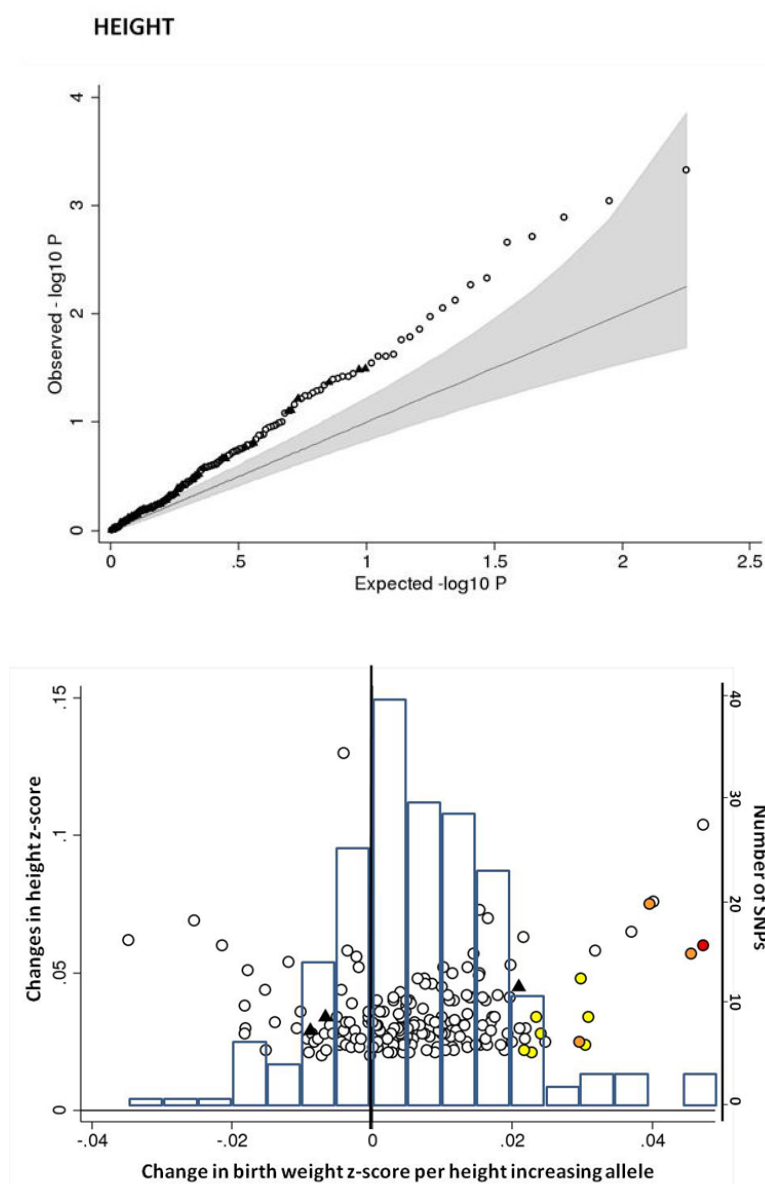
Regional plots of seven loci associated with birth weight at $P < 5 \times 10^{-8}$. For each of the *CCNL1* (a), *ADCY5* (b), *HMG2* (c), *CDKAL1* (d), *5q11.2* (e), *LCORL* (f), and *ADRB1* (g) regions, SNPs are plotted with their meta-analysis P values (as $-\log_{10}$ values) as a function of genomic position (NCBI Build 36). In each panel, the European discovery stage SNP taken forward for follow-up is represented by a purple circle (with global [discovery + follow-up] meta-analysis P value), with its discovery P value denoted by a purple diamond. Estimated recombination rates (taken from HapMap) are plotted to reflect the local LD structure around the associated SNPs and their correlated proxies (according to a blue to red scale from $r^2 = 0$ to 1, based on pairwise r^2 values from HapMap CEU). Gene annotations were taken from the University of California Santa Cruz genome browser.

TYPE 2 DIABETES



SYSTOLIC BLOOD PRESSURE



**Figure 2.**

Associations between birth weight and known type 2 diabetes (T2D; a and b), systolic blood pressure (SBP, c and d) or height (e and f) loci from the discovery meta-analysis of $N=26,836$ individuals. Plots a, c and e are quantile-quantile plots: the black triangles (associated with lower birth weight) and circles (associated with higher birth weight) represent observed P -values after removing the loci that achieved $P < 5 \times 10^{-8}$ in the overall meta-analysis, and the black line represents expected P -values under the null. The grey area defines the approximate 95% confidence interval around the expected line. Plots b, d and f show, respectively, the T2D, SBP or height effect size (left-hand y-axis), taken from published meta-analyses^{14,17,21,22}, against the birth weight effect size (x-axis), with a superimposed frequency histogram showing the number of SNPs in each category of birth weight effect size (right-hand y-axis). The odds ratios for type 2 diabetes are all obtained from the published DIAGRAM+ Consortium meta-analysis²², the largest available reference sample of European descent, and while they do not necessarily reach genome-wide

significance in that sample, all loci have shown associations with type 2 diabetes at $P < 5 \times 10^{-8}$ (see Online Methods for details of published studies). Effect sizes are aligned to the T2D risk allele or the SBP- or height-increasing allele. Colours indicate birth weight association P -values: $P < 5 \times 10^{-8}$ (red); $P \geq 5 \times 10^{-8}$ and $P < 0.001$ (orange); $P \geq 0.001$ and $P < 0.01$ (yellow); $P \geq 0.01$ (white). The triangles in plot f are SNPs known to be associated with age at menarche. There were more associations between height loci and higher birth weight than expected under the null, and a slight excess of associations between T2D or SBP loci and lower birth weight (binomial sign test $P = 0.02, 0.09$ and 3×10^{-10} for b, d and f, respectively).

Table 1

Associations between seven loci associated with birth weight and various anthropometric measures taken at birth (from joint meta-analysis of up to 69,308 individuals).

Locus (Index SNP, Effect allele/Other allele)	Birth weight (combined meta-analysis of European Discovery and Follow-up studies) [in grams]	Birth weight, adjusted for maternal genotype	Birth weight, adjusted for birth length	Birth length	Birth head circumference	Ponderal Index (weight/length ³)
<i>CCNL1</i> (rs900400, C/T)	N	61142	11130	35953	23000	35708
	Beta (SE)	-0.072 (0.006) [-35]	-0.108 (0.014)	-0.067 (0.005)	-0.033 (0.009)	-0.090 (0.008)
	P-value	3.6E-38	7.5E-14	1.2E-35	6.7E-04	9.5E-28
	Unadj beta (SE)*	-	-0.109 (0.013)	-0.085 (0.008)	-	-
	Unadj P-value*	-	7.5E-18	8.81E-29	-	-
<i>ADCY5</i> (rs9883204, C/T)	N	61509	11307	36084	23184	35836
	Beta (SE)	-0.059 (0.006) [-29]	-0.077 (0.016)	-0.032 (0.006)	-0.031 (0.010)	-0.034 (0.010)
	P-value	5.5E-20	1.5E-06	5.8E-07	0.0027	2.9E-04
	Unadj beta (SE)*	-	-0.064 (0.014)	-0.058 (0.009)	-	-
	Unadj P-value*	-	5.7E-06	7.4E-11	-	-
<i>HMG2</i> (rs1042725, T/C)	N	68655	9649	35961	23277	35781
	Beta (SE)	-0.047 (0.005) [-23]	-0.025 (0.015)	-0.018 (0.005)	-0.039 (0.009)	-0.016 (0.008)
	P-value	1.4E-19	0.096	5.5E-04	5.4E-06	0.049
	Unadj beta (SE)*	-	-0.029 (0.013)	-0.053 (0.007)	-	-
	Unadj P-value*	-	0.027	1.2E-12	-	-
<i>CDKALI</i> (rs6931514, G/A)	N	68822	9415	35789	22894	35614
	Beta (SE)	-0.050 (0.006) [-24]	-0.056 (0.017)	-0.026 (0.006)	-0.019 (0.010)	-0.034 (0.009)
	P-value	1.5E-18	0.001	9.4E-06	0.042	8.6E-05
	Unadj beta (SE)*	-	-0.045 (0.015)	-0.051 (0.008)	-	-
	Unadj P-value*	-	-	-	-	-

Locus (Index SNP, Effect allele/Other allele)	Birth weight (combined meta- analysis of European Discovery and Follow-up studies [in grams])			Birth weight, adjusted for maternal genotype	Birth weight, adjusted for birth length	Birth length	Birth head circumference	Ponderal Index (weight/length ³)
	Unadj	P-value	*					
<i>5q11.2</i> (rs4432842, C/T)	N	53619	6136	28465	28532	20222	28290	
	Beta (SE)	-0.034 (0.006)		-0.018 (0.006)	-0.023 (0.008)	-0.030 (0.010)	-0.023 (0.009)	
	P-value	4.6E-08		0.003	0.006	0.003	0.010	
	Unadj beta (SE)	-		-0.043 (0.018)	-	-	-	
	Unadj P-value	-		0.018	4.6E-05	-	-	
<i>LCORL</i> (rs724577, C/A)	N	55877	8733	29956	30027	21065	29781	
	Beta (SE)	-0.042 (0.006)		-0.010 (0.006)	-0.047 (0.009)	-0.027 (0.010)	-0.011 (0.010)	
	P-value	4.6E-11		2.0E-05	0.13	8.3E-08	0.258	
	Unadj beta (SE)	-		-0.071 (0.016)	-0.042 (0.009)	-	-	
	Unadj P-value	-		8.4E-06	3.8E-06	-	-	
<i>ADRB1</i> (rs1801253, G/C)	N	49660	6231	29695	29762	17833	29519	
	Beta (SE)	-0.041 (0.007)		-0.029 (0.023)	-0.027 (0.009)	-0.033 (0.011)	-0.035 (0.009)	
	P-value	3.6E-09		0.18	0.001	0.004	2.3E-04	
	Unadj beta (SE)	-		-0.036 (0.019)	-0.045 (0.009)	-	-	
	Unadj P-value	-		0.058	4.3E-07	-	-	

Results are from inverse variance, fixed-effects meta-analysis of all available study samples of European ancestry. The effect allele for each SNP is labelled on the positive strand according to HapMap. The beta value is the change in trait z score per birth weight-lowering allele from linear regression, adjusted for sex and gestational age (where available), assuming an additive genetic model. To obtain the equivalent birth weight effect in grams, we multiplied by 484g, the median birth weight standard deviation of European studies in ². There was little detectable heterogeneity between studies (all $P > 0.01$).

* Results are unadjusted for maternal genotype or birth length, but only in samples where maternal genotype or birth length is available (for direct comparison with the model that is adjusted for maternal genotype or birth length, respectively.)